

J. Perinat. Med.  
16 (1988) 45

## High permeability pulmonary edema (ARDS) during tocolytic therapy — a case report\*

Erich W. Russi<sup>1</sup>, Ludwig Spaetling<sup>2</sup>, Jürg Gmür<sup>1</sup>, and Henning Schneider<sup>2</sup>

Department of Internal Medicine<sup>1</sup> and Department of Obstetrics<sup>2</sup>, University Hospital, Zurich, Switzerland

### 1 Introduction

The therapeutic value of fenoterol and other predominantly beta-sympathomimetic agents for the treatment of premature labor is undisputed [11]. Recently several cases of pulmonary edema have been reported in patients with beta-sympathomimetic agents alone or in combination with corticosteroids [1, 2, 4, 8, 9, 10, 12, 18]. The mechanism of the development of pulmonary edema in women in premature labor and with tocolytic treatment remains speculative. Our observation suggests that in some cases increased pulmonary capillary permeability may be a likely mechanism.

### 2 Case report

A 26-year old woman, with 4 interruptions of pregnancy in her history was admitted because of premature labor at 30 weeks pregnancy. Her past medical history was unremarkable and physical examination was normal. The following values were recorded for vital signs: blood pressure 100/60 torr; pulse 84 beats/min; respiration 16 breaths/min. The chest was clear to auscultation and percussion and no murmur or gallop rhythm was noted. ECG was normal. Because of regular contractions persisting four hours after admission with effacement of the cervix and beginning dilatation of 2 cm a continuous infusion of fenoterol at a rate of 2 µg/min together with low-dose magnesium-sulfate/magnesium-aspartate-hydrochloride (40 mmol/24 hours) for cardioprotection was started [17]. There was no oral fluid restriction

### Curriculum vitae

Dr. E. W. Russi is Oberarzt at the Department of Internal Medicine, University Hospital, Zurich. He trained in internal medicine in Solothurn and Zurich as well as in neurology at the Inselspital, Bern. He worked as a clinical and research fellow for two years at the pulmonary Division of Mount Sinai Medical Center in Miami Beach, Fla. USA. His major research interest is bronchial hyperreactivity.



and parenteral fluid was administered at a rate of 60 ml/h.

Furthermore the patient received two intravenous injections of 12 mg of bethamethasone 12 hours apart. On the following day spontaneous rupture of membranes was noticed. Because of a hemoglobin of 9.7 g/100 ml two units of packed red cells were transfused over a period of 6 hours. At the end of the transfusion the patient started to complain about a tight feeling in her chest and two hours later she became short of breath. The pulse rate was 96 beats/min the respiratory rate increased to 40 breaths/min and the patient became slightly cyanotic despite 4 l/min of oxygen. The temperature at this point was 37.6 °C, and the heart rate 140/min. Arterial blood gases while receiving oxygen at 8 l/min were  $P_{O_2}$ : 33 torr,  $P_{CO_2}$ : 34.8 torr, and pH: 7.41. Tocolytic therapy was stopped immediately. Chest-x-ray was consistent with alveolar pulmonary edema. Treatment

\* See also Comment on page 50.

with furosemide, digoxin and nitroglycerin was started but with no significant effect. The total urine output during the first five hours following treatment was 570 ml. Because of further deterioration, the patient had to be intubated and ventilated. For induction of labor an intravenous infusion of PGE<sub>2</sub> was started. Because of signs of fetal distress in the fetal heart rate tracing, a male of 1220 g was delivered by low forceps with an Apgar score of 2 at 1 min, 4 at 5 min and 7 at 10 min with an umbilical artery pH of 7.12.

Three hours after delivery the infant could be extubated and remained in good condition. After blood cultures had been obtained treatment with amoxycillin and gentamicin was started which could be stopped after 48 hours since cultures remained negative. Suddenly on the fifth postpartum day the condition of the previously healthy infant deteriorated with clinical signs of sepsis. In spite of aggressive treatment with antibiotics, immunoglobulins and mechanical ventilation there was rapid progression and the infant died on the sixth day. Blood as well as cerebrospinal fluid cultures grew klebsiellae suggesting a nosocomial infection.

In view of early signs of chorioamnionitis the mother was started on ceftriaxon and she was transferred to the medical ICU. A Swan-Ganz catheter was inserted; right atrial pressure was 5 mmHg; right ventricle 25/5 mmHg; pulmonary artery 25/12 mmHg; wedge pressure 10 mmHg; cardiac output as measured by thermo-dilution was 4.4 l/m<sup>2</sup>/min. The electrocardiogram was normal. Ventilator settings, arterial blood gas analysis and total thoracic quasi static compliance (employing the formula described by BONE [3]) are summarized in table I. The analysis of the tracheo-bronchial secretion revealed a protein content of 6.4 g/100ml (plasma: 6.1 g/100ml) with 3.29 g/

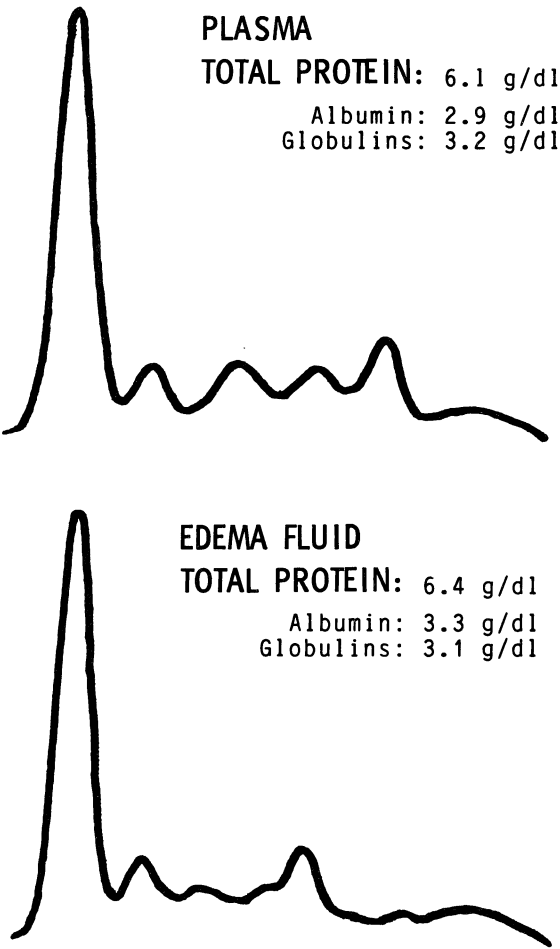


Figure 1. Protein electrophoresis of plasma and lung edema fluid.

100ml albumin (plasma: 2.94 g/100ml) (figure 1). On gram stains no microorganisms were seen and blood cultures remained sterile.

Table I. Ventilator settings and resulting arterial blood gases.

Date	time	FIO <sub>2</sub>	TV	f	PEEP	Po <sub>2</sub> *	Pco <sub>2</sub> *	pH	C <sub>st</sub>
29. 7.	7.15	1.0	900	12	10	68	43.5	7.35	37
	12.30	0.5	800	10	7.5	75	53.3	7.41	64
30. 7.	8.30	0.3	800	10	5	119	29.0	7.46	53
	11.00	0.3	800	10	0	107	28.5	7.46	66
1. 8.	8.00	0.21	spontaneous			71	33.0	7.43	—

FIO<sub>2</sub>: fractional inspiratory oxygen concentration; TV: tidal volume (ml); f: respiration rate (breaths/min); PEEP: positive endexpiratory pressure (cmH<sub>2</sub>O); C<sub>st</sub>: quasi-static compliance (ml/cmH<sub>2</sub>O). \*: Torr.

Serum electrolytes including calcium and magnesium, creatinine, blood urea nitrogen and glucose were normal as well as all coagulation parameters and there were no signs of increased fibrinolysis. The hemoglobin was 13.6 g/100 ml, leucocytes 15'500 with 27.5% bands, 55% segments, 0.5% eosinophils, 1.0% basophils, 5.0% monocytes and 11.0% lymphocytes. Because of initial suspicion of sepsis, piperacillin and netromycin were administered under blood level monitoring. The patient's respiratory condition improved rapidly and she was extubated after 36 hours of ventilatory support. During this time she had received a total of 3060 ml of intravenous fluids and her urine output was 2650 ml. Her chest roentgenogram cleared completely and pulmonary function analysis eight days later revealed normal static and dynamic lung volumes. An idiopathic hypertrophic aortic stenosis or other cardiac abnormalities were excluded by an echocardiography. The patient's blood group was 0 Rh positive. The serum was tested for red cell antibodies and demonstrated negative standard compatibility tests with red cells of both donors. The patient's serum and the serum of both donors were further tested for lymphocyte and granulocyte cytotoxicity (directly and in white cell panel). All these tests were negative.

### 3 Discussion

Fenoterol and other beta-sympathomimetic agents are widely used for the treatment of premature labor. These agents increase maternal pulse rate and cardiac output and cause peripheral vasodilatation. In addition they have an antidiuretic effect with retention of sodium and water [7]. Although pulmonary edema has been infrequently reported [1, 2, 4, 8, 9, 10, 12, 18], it is a serious complication that has even resulted in maternal death [1]. Since beta-sympathomimetic agents may further increase the physiologic high output state of pregnancy it has been speculated that the most likely cause of pulmonary edema is heart failure triggered or aggravated by fluid overload [1, 8, 18]. Although chest pain and electrocardiographic changes consistent with myocardial ischemia have been reported during terbutaline treatment in young women with presumably normal coronary arteries [9] an echocardiographic study demonstrated increases in left ventricular function parameters even in a patient who developed clinically manifest pulmonary edema [21]. These data sug-

gest that pulmonary edema probably is not due to left ventricular failure. In most of the reported cases a positive fluid balance was documented before the development of pulmonary edema and the respiratory symptoms would markedly improve after the induction of diuresis so that fluid overload might play a crucial role as a trigger [8, 9]. The respiratory distress which developed under tocolytic therapy in this 26-year old women apparently was of a different nature and fulfills the criteria of an adult respiratory distress syndrome (ARDS). ARDS is commonly defined as a clinical pathophysiologic condition of sudden onset characterized by progressive dyspnea, severe hypoxemia which is relatively refractory to high inspiratory oxygen concentrations, diffuse pulmonary infiltrates, and "stiff lungs". It may develop following a variety of acute lung injuries, usually in persons with no prior lung disease [13]. Of specific interest to the obstetrician are eclampsia, sepsis, aspiration and amniotic fluid embolism as possible underlying causes. Clinical symptomatology is often inadequate to differentiate between cardiogenic pulmonary edema and ARDS since the usual clinical findings are remarkably similar.

The central pathophysiologic feature of ARDS is increased permeability of the alveolar-capillary membranes with resultant progressive interstitial and alveolar edema. The measurement of pulmonary capillary wedge pressure (reflecting left ventricular filling pressure) by a Swan-Ganz balloon flotation catheter permits to differentiate between this condition and cardiac causes. In ARDS, although pulmonary arterial pressure and pulmonary vascular resistance may be elevated, the capillary pressure remains normal or low. To our knowledge this is the first case where the diagnosis of high permeability pulmonary edema occurring under tocolytic therapy was firmly established by simultaneous hemodynamic measurements and protein analysis of pulmonary edema fluid. Recently there has been another report of ARDS as a complication of pyelonephritis in pregnancy [5]. Although tocolysis with beta-sympathomimetic agents was also applied endotoxin mediated injury of the pulmonary capillaries may have contributed to the development of ARDS in that case. Animal studies in which alveolar fluid was obtained by direct alveolar micropuncture have shown that the protein concentration of alveolar fluid is similar to that of fluid in the airways in both cardiac and permeability types of pulmonary edema [19, 20]. Clinical studies have shown that the analysis of

edema protein relative to plasma protein concentrations is useful in separating these two types of pulmonary edema. In a study by FEIN et al. [6] the mean edema fluid to plasma total protein ratio was 0.94 in patients without clinical or hemodynamic evidence of cardiovascular disease as opposed to a mean ratio of 0.46 in patients with cardiogenic pulmonary edema.

Although our patient received two units of blood before the onset of dyspnea, we do not see a causal relation with the development of pulmonary edema. The improvement of gas exchange and the clearance of the pulmonary infiltrates were not preceded or accompanied by a negative fluid balance. Furthermore, the transfusion of blood would lead to an expansion of the intravascular volume with an increase in left ventricular filling pressure and not to pulmonary capillary leakage. Pulmonary edema may be induced by blood transfusion as a consequence of mechanisms other than circulatory overload. Immunologic reactions against granulocytes due to previous sensitization

or by passively transfused antibodies leading to pulmonary edema have been reported [14, 15]. Careful immuno-hematological work-up of our patient and the two blood donors had excluded this possibility.

The hypothesis that at least some of the cases of pulmonary edema during tocolytic treatment are due to a transient increase in pulmonary capillary permeability is supported by the measurement of normal pulmonary capillary pressure by other investigators [2, 10]. Furthermore, we have experimental evidence that beta-sympathomimetic decrease the carbon monoxide diffusion capacity in the lungs of healthy volunteers which would indicate a direct effect on the alveolar-capillary membranes [16].

The contribution of the various factors like defects in the alveolar-capillary membrane, fluid overload, blood transfusion and corticosteroids for the development of the full blown clinical picture of pulmonary edema will vary in different cases.

## Abstract

A 26 year old previously healthy woman who was treated with fenoterol for premature labor at 30 gestational weeks developed pulmonary edema requiring intubation and mechanical ventilation. Vaginal delivery was accomplished with forceps after tocolytic therapy had been stopped. Right heart catheterization with measurement of pulmonary wedge pressure did not reveal left ventricular failure. Protein determination in

lung edema fluid provided evidence of increased pulmonary capillary permeability. Recovery was rapid and ventilatory support was stopped after 36 hours. It is suggested that the infusion of beta-sympathomimetic drugs may alter the permeability of the alveolar-capillary membranes which together with triggering factors such as fluid overload might lead to clinically manifest pulmonary edema.

**Keywords:** ARDS, high permeability, pulmonary edema, tocolysis.

## Zusammenfassung

### Permeabilitätslungenoedem (ARDS) unter tokolytischer Therapie

Eine 26jährige, vorher gesunde Frau wurde wegen vorzeitiger Wehen in der dreißigsten Schwangerschaftswoche mit einer Tropfinfusion des beta<sub>2</sub>-Mimetikums Fenoterol behandelt. Wegen der Entwicklung einer respiratorischen Insuffizienz bei Lungenödem war eine Intubation und maschinelle Beatmung notwendig. Die tokolytische Behandlung wurde gestoppt und die Patientin vaginal mittels Zange entbunden. Der durchgeführte Rechtsherzkatheter ergab keinen Anhaltspunkt für eine

Linksherz-Insuffizienz. Der hohe Proteingehalt der abgesaugten Lungenödem-Flüssigkeit deutete auf eine erhöhte Permeabilität der Lungenkapillaren hin. Die Patientin erholte sich ausgesprochen rasch, so daß sie nach 36 Stunden extubiert werden konnte. Es ist möglich, daß die Infusion eines beta<sub>2</sub>-Adrenergikums in der Schwangerschaft die Permeabilität der alveolo-kapillären Membran erhöht, so daß es vor allem dann, wenn zusätzliche Momente wie z. B. eine Flüssigkeitsüberladung vorliegen, zum Auftreten eines klinisch manifesten Lungenödems kommen kann.

**Schlüsselwörter:** ARDS, Lungenödem, Permeabilitätserhöhung.

## Résumé

### Œdème pulmonaire à haute perméabilité (A. R. D. S.) au cours du traitement tocolytique

Une patiente de 26 ans jusqu'alors en bonne santé, traitée par du Fénotérol pour une menace d'accouchement prématuré à 30 semaines a présenté un œdème pulmonaire nécessitant une intubation et une ventilation artificielle. Un accouchement par voie basse avec application de forceps s'est déroulé après l'arrêt de la tocolyse. Un cathétérisme droit avec mesure des pressions pulmonaires n'a pas mis en évidence de défaillance ventriculaire

gauche. La recherche de protéines dans le liquide d'œdème pulmonaire a apporté la preuve d'une augmentation de la perméabilité capillaire pulmonaire. La guérison a été rapide et l'assistance ventilatoire a pu être interrompue au bout de 36 heures. Les auteurs suggèrent que la perfusion de bêta-2-mimétiques peut altérer la perméabilité des membranes alvéolo-capillaires ce qui en liaison avec des facteurs déclenchants tels qu'une surcharge liquidienne peut conduire à un œdème pulmonaire manifeste cliniquement.

**Mots-clés:** A.R.D.S., œdème pulmonaire, perméabilité élevée, tocolyse.

## References

- [1] BENDER HG, G GOECKENJAN, C MEGER: Zum mütterlichen Risiko der medikamentösen Tokolyse mit Fenoterol (Partusisten). *Geburtshilfe Frauenheilkd* 37 (1977) 665
- [2] BENETTI TJ, JC HARGOVE, KA ROSENE: Maternal pulmonary edema during premature labor inhibition. *Obstet Gynecol* 59 (1982) 33S
- [3] BONE R: Thoracic pressure-volume curves in respiratory failure. *Crit Care Med* 4 (1976) 148
- [4] DAVIES AE, MJS ROBERTSON: Pulmonary edema after administration of intravenous salbutamol and ergometrine. *Br J Obstet Gynecol* 87 (1980) 539
- [5] ELKINGTON KW, LC GREB: Adult respiratory distress syndrome as a complication of acute pyelonephritis during pregnancy: case report and discussion. *Obstet Gynecol* 67 (1986) 18S
- [6] FEIN A, RF GROSSMANN, JG JONES, E OVERLAND, L PITTS, JF MURRAY, NC STAUB: The value of edema fluid protein measurement in patients with pulmonary edema. *Am J Med* 67 (1979) 32
- [7] GROSPIETSCH G, M FENSKE, W KUHN: Zur Frage des Lungenödems bei der tokolytischen Therapie. *Geburtshilfe Frauenheilkd* 40 (1980) 55
- [8] JAKOBS JM, AB KNIGHT, F ARIA: Maternal pulmonary edema resulting from betamimetic and glucocorticoid therapy. *Obstet Gynecol* 56 (1980) 56
- [9] KATZ M, PA ROBERTSON, RK CREASY: Cardiovascular complications associated with terbutaline treatment for preterm labor. *Am J Obstet Gynecol* 139 (1981) 605
- [10] MABIE WC, ML PERNOLL, JB WITTY: Pulmonary edema induced by betamimetic drugs. *South Med J* 76 (1983) 1354
- [11] MERKATZ IR, JB PETER, TP BARDEN: Ritodrine hydrochloride: A betamimetic agent for use in preterm labor. *Obstet Gynecol* 56 (1980) 7
- [12] NIMROD C, V RAMBIHAR, E FALLEN: Pulmonary edema associated with isoxduprine therapy. *Am J Obstet Gynecol* 148 (1984) 625
- [13] PETTY LT: Adult respiratory distress syndrome: definition and historical perspective. *Clin Chest Med* 3 (1982) 3
- [14] PHILIPPS E, FG FLEISCHER: Pulmonary edema in the course of a blood transfusion without overloading the circulation. *Dis Chest* 50 (1966) 619
- [15] POPOVSKY MA, MD ABEL, SB MOORE: Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. *Am Rev Respir Dis* 128 (1983) 185
- [16] SPAETLING L, KJ STAISCH, R HUCH, A HUCH: Effect of ritodrine and betamethasone on metabolism, respiration and circulation. *Am J Perinatol* 3 (1986) 41
- [17] SPAETLING L: Magnesiumzusatztherapie zur Tokolyse: Klinisch-chemische Überwachungsparameter. *Geburtshilfe Frauenheilkd* 44 (1984) 19
- [18] STUBBLEFIELD PG: Pulmonary edema occurring after therapy with dexamethasone and terbutaline for premature labor: A case report. *Am J Obstet Gynecol* 132 (1978) 341
- [19] VREIM CE, PD SNASHALL, NC STAUB: Protein composition of lung fluids in anesthetized dogs with acute cardiogenic edema. *Am J Physiol* 231 (1976) 1466
- [20] VREIM CE, NC STAUB: Protein composition of lung fluids in acute alloxan edema in dogs. *Am J Physiol* 230 (1976) 376
- [21] WAGNER JM, MJ MORTON, KA JOHNSON, JP O'GRADY, L SPEROFF: Terbutaline and maternal cardiac function. *JAMA* 246 (1981) 2697

Received January 2, 1986. Revised July 3, 1986.  
Accepted February 10, 1987.

Dr. E. Russi  
Department of Internal Medicine  
University Hospital  
Raemistrasse 100  
CH-8091 Zürich, Switzerland